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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 487/00

A2

(11) International Publication Number: **WO 00/06575**

(43) International Publication Date: 10 February 2000 (10.02.00)

(21) International Application Number: PCT/EP99/05350

(22) International Filing Date: 23 July 1999 (23.07.99)

(30) Priority Data:

| | | |
|---|---|---|
| 9816288.6 | 28 July 1998 (28.07.98) | GB |
| 9827881.5 | 17 December 1998 (17.12.98) | GB |


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(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

**Published**

*Without international search report and to be republished upon receipt of that report.*

(54) Title: NOVEL COMPOUNDS

(57) Abstract

The invention relates to novel azabicyclic compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS disorders.

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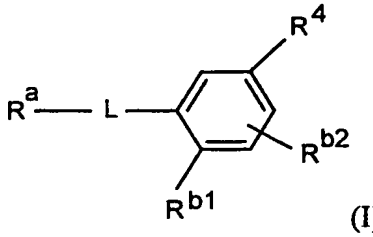
# NOVEL COMPOUNDS

The present invention relates to novel azabicyclic compounds, processes for their preparation, and pharmaceutical compositions containing them.

US patent 5,703,072 discloses bicyclic nonane and decane compounds having dopamine receptor affinity which are claimed to be of use in the treatment of schizophrenia. WO 95/04729, WO 95/06044 and WO 95/06637 all disclose a series of piperazine derivatives which are said to possess $5HT_{1D}$ receptor antagonist activity. EPA 0533266/7/8 disclose a series of benzanilide derivatives which are said to possess 5-$HT_{1D}$ receptor antagonist activity. The 5-$HT_{1D}$ receptor was subsequently found to consist of a pair of gene products originally designated 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors which have more recently been reclassified as 5-$HT_{1D}$ and 5-$HT_{1B}$ receptors, respectively. (Hartig, P.R. et al., Trends in Pharmacological Sciences 1992, Vol. 13, page 152, Hartig, P.R. et al., Trends in Pharmacological Sciences, 1996, Vol. 17, page 103).

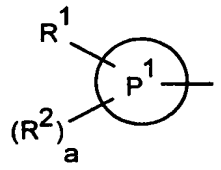
A structurally distinct class of compounds have now been found that exhibit combined $5HT_{1A}$, $5HT_{1B}$ and $5HT_{1D}$ receptor affinity. It is expected that such compounds will be useful for the treatment and prophylaxis of various disorders. In a first aspect, the present invention therefore provides a compound of formula (I) or a salt thereof:




(I)

in which $R^a$ is selected from a group of formula (i), (ii) or (iii):

Group of formula (i)




(i)

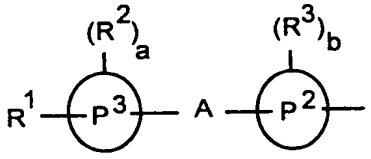
in which $P^1$ is phenyl, bicyclic aryl, a 5- to 7- membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur or a bicyclic heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur;

$R^1$ is hydrogen, halogen, $C_{1-6}$alkyl, $C_{3-6}$cycloalkyl, $C_{1-6}$alkanoyl, $C_{1-6}$alkoxy, hydroxy, hydroxy$C_{1-6}$alkyl, hydroxy$C_{1-6}$alkoxy, $C_{1-6}$alkoxy$C_{1-6}$alkoxy, nitro, trifluoromethyl, cyano, $SR^9$, $SOR^9$, $SO_2R^9$, $SO_2NR^{10}R^{11}$, $CO_2R^{10}$, $CONR^{10}R^{11}$, $CONR^{10}(CH_2)_cCO_2R^{11}$, $(CH_2)_cNR^{10}R^{11}$, $(CH_2)_cCONR^{10}R^{11}$, $(CH_2)_cNR^{10}COR^{11}$, $(CH_2)_cCO_2C_{1-6}$alkyl, $CO_2(CH_2)_cOR^{10}$, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CONR^{10}R^{11}$, $CR^{10}=NOR^{11}$ where $R^9$, $R^{10}$ and $R^{11}$ are independently hydrogen or $C_{1-6}$alkyl and c is 1 to 4;

$R^2$ is halogen, $C_{1-6}$alkyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkenyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, aryl. -$OC(O)C_{1-6}$alkyl, hydroxy, nitro, trifluoromethyl, cyano, $CO_2R^{10}$, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where $R^{10}$ and $R^{11}$ are as defined for $R^1$;

a is 0, 1 or 2;

Group of formula (ii)




(ii)

wherein $P^2$ and $P^3$ are independently phenyl, bicyclic aryl, a 5- to 7- membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a bicyclic heterocyclic group containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur;

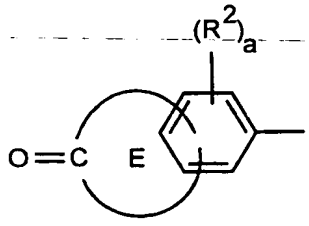
A is a bond or oxygen, $S(O)_n$ where n is 0 to 2, carbonyl, $CH_2$ or $NR^4$ where $R^4$ is hydrogen or $C_{1-6}$alkyl;

$R^1$ is as defined above for formula (i) or is a 5 to 7-membered heterocyclic ring, containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur, optionally substituted by $C_{1-6}$alkyl, halogen or $C_{1-6}$alkanoyl;

$R^2$ and $R^3$ are as defined above for $R^2$ in formula (i);

and a and b are independently 0, 1 or 2;

Group of formula (iii)




(iii)

in which the ring E is a 5, 6 or 7 -membered carbocyclic ring optionally substituted by one or more $C_{1-6}$alkyl groups, fused at the 2,3- or 3,4-positions of the adjacent phenyl ring, the ring E being optionally fused to a further phenyl ring optionally substituted by one or more substituents independently selected from $C_{1-6}$alkyl and halo;

a is 0, 1 or 2; and

$R^2$ is as defined above for formula (i);

L is a group of formula

- C (=V) - DG - or - DG - C(=V) - or -Y-C(=V)-DG-

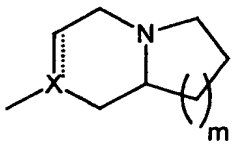
V is oxygen or sulphur;

Y is -NH- or -$NR^5$- where $R^5$ is $C_{1-6}$alkyl, or Y is -$CH_2$- or -O-;

D is nitrogen, carbon or a CH group, G is hydrogen or $C_{1-6}$alkyl, providing that D is nitrogen or a CH group, or G together with $R^{b1}$ forms a group W where W is $(CR^{16}R^{17})_t$ where t is 2, 3 or 4 and $R^{16}$ and $R^{17}$ are independently hydrogen or $C_{1-6}$alkyl or W is $(CR^{16}R^{17})_u$-J where u is 0, 1, 2 or 3 and J is oxygen, sulphur, $CR^{16}=CR^{17}$, $CR^{16}=N$, $=CR^{16}O$, $=CR^{16}S$ or $=CR^{16}-NR^{17}$ provided that u is not 0 when J is oxygen or sulphur;

$R^{b1}$ and $R^{b2}$ are independently hydrogen, halogen, hydroxy, $C_{1-6}$alkyl, trifluoromethyl, $C_{1-6}$alkoxy or aryl, or $R^{b1}$ together with G forms a group W as defined above;

$R^4$ is a group of formula (a) optionally substituted by $C_{1-6}$alkyl;



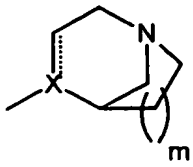

(a)

in which X is nitrogen, carbon or a CH,

..... is a single bond when X is nitrogen or CH and is a double bond when X is carbon,

m is 1, 2 or 3 ;

or $R^4$ is a group of formula (b) optionally substituted by $C_{1-6}$alkyl;




(b)

in which ....., X and m are as defined in formula (a);

$C_{1-6}$alkyl groups whether alone or as part of another group may be straight chain or branched. The term 'aryl' is used herein to describe, unless otherwise stated, a group such as phenyl or naphthyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The bicyclic aryl group represented by $P^1$, $P^2$ and/or $P^3$, which may be partially saturated, is preferably naphthyl.

The bicyclic heterocyclic rings represented by $P^1$, $P^2$ and/or $P^3$ may also be partially saturated. Examples of bicyclic heterocyclic rings include quinoline, isoquinoline, indole, benzofuran, benzothiazole and benzothiadiazole. The heterocyclic groups can be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom.

Examples of 5 to 7 membered heterocyclic rings containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur represented by $P^1$, $P^2$ and/or $P^3$, include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrimidyl, pyrazinyl and most preferably pyridyl.

$R^1$ is preferably hydrogen, a $C_{1-6}$alkyl group for example a methyl group or a halogen atom for example, fluorine, chlorine or bromine. $R^2$ and/or $R^3$ are each preferably a $C_{1-6}$alkyl group for example a methyl group or a halogen atom for example, fluorine, chlorine or bromine.

a and b are each preferably 0 or 1.

Within the definition of $R^a$ formula (ii), A is preferably a bond.

Within the definition of $R^a$ formula (iii) the ring E, in addition to the keto group and the portion fused to the phenyl ring, is preferably formed from a straight chain alkylene grouping containing 2, 3 or 4 carbon atoms. The ring E is preferably a 5 or 6-membered ring in which the oxo group is advantageously attached to a carbon atom adjacent to the phenyl ring, the ring E being preferably attached to the 3,4-positions of the latter phenyl ring.

Most preferably $R^a$ is a group of formula (ii) wherein $P^2$ is naphthyl and $P^3$ is pyridyl.

In the group L, as defined above:-

V is preferably oxygen.

D is preferably nitrogen and G is preferably a hydrogen atom or together with $R^{b1}$ forms a group W, preferably $-(CH_2)_2-$.

$R^{b1}$ is preferably hydrogen or together with G forms a group W as above.

$R^{b2}$ is preferably hydrogen, halogen for example chlorine, or a $C_{1-6}$alkoxy group for example methoxy. Preferably the group $R^{b2}$ has a para relationship with respect to the group $R^a$-L.

Within the definition of $R^4$ formulas (a) and (b), X is preferably a nitrogen atom, and m is preferably 1 or 2. The group $R^4$ can be substituted by 1, 2 or 3 $C_{1-6}$alkyl groups such as methyl. Preferably the group $R^4$ is unsubstituted.

Particularly preferred compound according to the invention are:-

N-[(S)-4-Methoxy-3-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)phenyl]-N'-[4-(pyridin-4-yl)naphth-1-yl]-urea,

(S)-(-)-5-Methoxy-1-[5-(6-methylpyridin-2-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline,

(S)-(-)-5-Methoxy-1-[5-(2-methylpyridin-3-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline,

(S)-(-)-1-[5-(2,6-Dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-5-methoxy-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline,

(S)-(-)-1-[5-(2,6-Dimethylpyridin-3-yl)naphth-1-ylaminocarbonyl]-5-methoxy-6-(octahydropyrrolo[1,2-a]pyrazin-2-yl)indoline,

(R)-(+)-1-[5-(2,6-Dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-5-methoxy-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline,

(R/S)-(+/-)-1-[5-(2,6-Dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-5-methoxy-6-(octahydropyrido[1,2-*a*]pyrazin-2-yl)indoline,

6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-1-[5-(2,6-dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-5-methoxyindoline,

(S)-(-)-1-[5-(6-Methylpyridin-2-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline,

(S)-(-)-5-Chloro-1-[5-(6-methylpyridin-2-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline,

(S)-(-)-5-Chloro-1-[5-(6-methylpyridin-3-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline,
(S)-(-)-5-Chloro-1-[5-(2,6-dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline
and pharmaceutically acceptable salt thereof.

Preferred salts of the compounds of formula (I) are pharmaceutically acceptable salts. These include acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and the mixtures thereof including racemates.

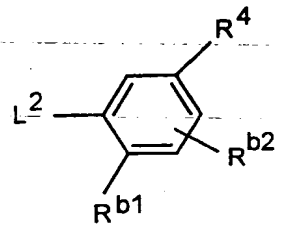
Compounds of the invention can be prepared using procedures known in the art. In a further aspect the present invention provides a process for the preparation of a compound of formula (I) which comprises:

(a) where L is - C (=V) - DG - or - DG - C(=V) -, coupling a compound of formula (II):

$$R^a\text{-}L^1$$

(II)

with a compound of formula (III)



(III)

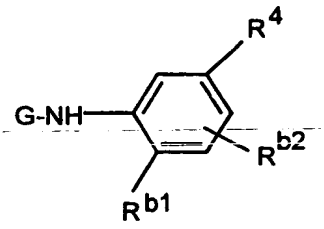
in which $R^a$, $R^{b1}$, $R^{b2}$, $R^4$ are as defined in formula (I) and $L^1$ and $L^2$ contain the appropriate functional groups which are capable of reacting together to form the L moiety; or

(b) where L is - Y -C(=V)-DG in which D is nitrogen and Y is NH, coupling a compound of formula (IV):

$$R^a\text{-}NC(=V)$$

(IV)

in which $R^a$ and V are as defined in formula (I) or a protected derivative thereof with a compound of formula (V); or




(V)

in which $R^{b1}$, $R^{b2}$, $R^4$, G are as defined in formula (I), or a protected derivative thereof; or

(c) where L is - Y -C(=V)-DG - in which D is nitrogen and Y is NH or $NR^5$, reacting a compound of formula (VI)

$$R^a\text{-}NH_2 \text{ or } R^a\text{-}NR^5H$$

(VI)

in which $R^a$ and $R^5$ are as defined in formula (I) with a compound of formula (V) together with an appropriate urea forming agent; or

(d) where L is - Y -C(=V)-DG - in which D is nitrogen and Y is $CH_2$ or O, reacting a compound of formula (VII)

$$R^a\text{-}Y\text{-}(C{=}O)\text{-}L^3$$

(VII)

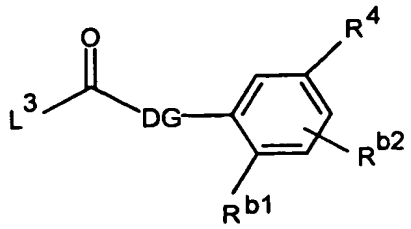
in which $R^a$ is as defined in formula (I),
and $L^3$ is an appropriate leaving group, with a compound of formula (V); or

(e) where L is - Y -C(=V)-DG – in which D is CH and Y is NH, reacting a compound of formula (VI)

$$R^a\text{-}NH_2$$

(VI)

in which $R^a$ is as defined in formula (I) with a compound of formula (VIII)



(VIII)

in which D is CH, and G, $R^4$, $R^{b1}$ and $R^{b2}$ are as defined in formula (I) and $L^3$ is an appropriate leaving atom

and optionally thereafter:

- removing any protecting groups,
- converting a compound of formula (I) into another compound of formula (I),
- forming a pharmaceutically acceptable salt.

In the reaction of the compounds of formulae (II) and (III), suitable examples of groups $L^1$ and $L^2$ include:-

$L^1$ is $COL^a$ and $L^2$ is $NH_2$

$L^1$ is $NH_2$ and $L^2$ is $COL^a$

in which $L^a$ is an appropriate leaving group.

Suitably one of $L^1$ and $L^2$ is an activated carboxylic acid derivative such as an acyl chloride or acid anhydride, and the other is an amine group. Activated compounds of formulae (II) and (III) can also be prepared by reaction of the corresponding carboxylic acid with a coupling agent such as dicyclohexylcarbodiimide, carbonyldiimidazole or diphenylphosphorylazide. Preferably $L^1$ or $L^2$ is a group $COL^a$ where $L^a$ is halo particularly chloro.

Compounds of formulae(II) and (III) are typically reacted together in an inert solvent such as dimethylformamide, tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as an alkali metal hydroxide,triethylamine or pyridine.

The reaction in process (b) is conveniently effected in an organic solvent such as dichloromethane.

In process (c) the urea forming agent can be carbonyl diimidazole, triphosgene or phosgene, and carried out in an inert organic solvent such as dimethylformamide, tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

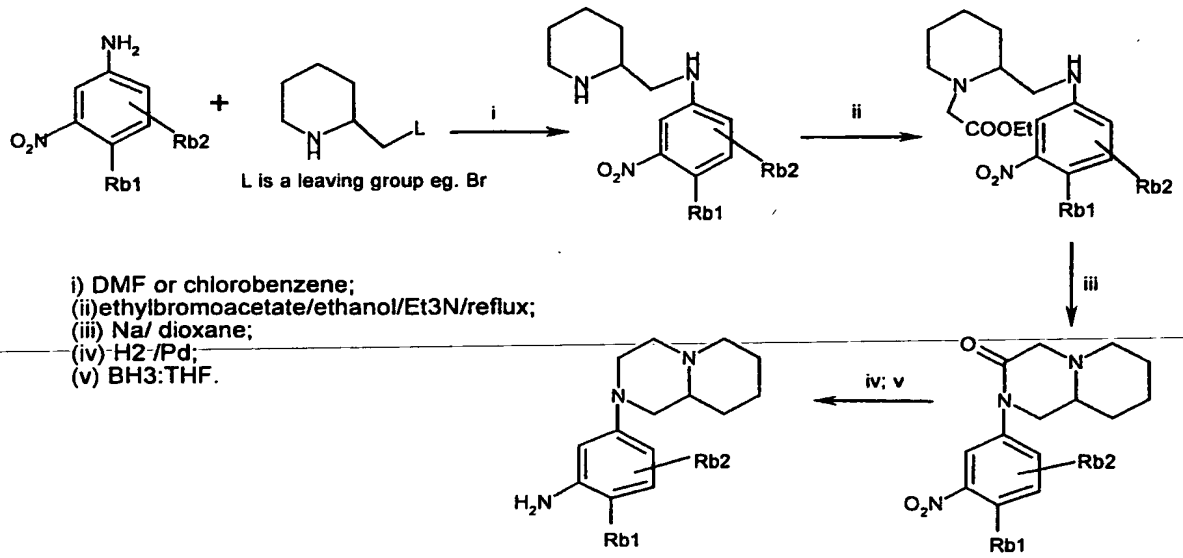
In processes (d) and (e) the leaving atom $L^3$ is a halogen atom e.g. chloro group, and the reaction may be carried out in an inert organic solvent such as tetrahydrofuran or

dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

Intermediate compounds of formula (II) can be prepared using standard procedures known in the art.

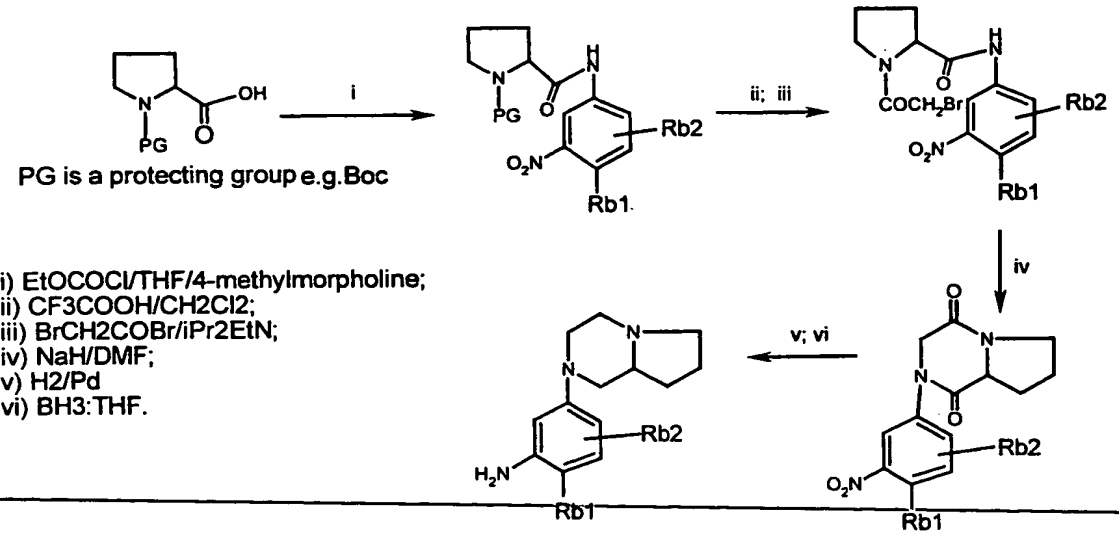
Intermediate compounds of formula (III) and (V) can be synthesized using established synthetic techniques from starting materials that are either commercially available or known compounds. For example, aryl octahydro-2H-pyrido[1,2-*a*]pyrazines intermediates can be obtained by a synthetic procedure as represented by scheme 1.

Scheme 1




A modified strategy, based on the use of a suitably protected proline derivatives, can be used to prepare aryl octahydropyrrolo[1,2-a]pyrazines intermediates of general formula (III) or (V) using a synthetic procedure as represented by scheme 2. It is noted that both enantiomers can be prepared starting from the appropriate chiral proline.

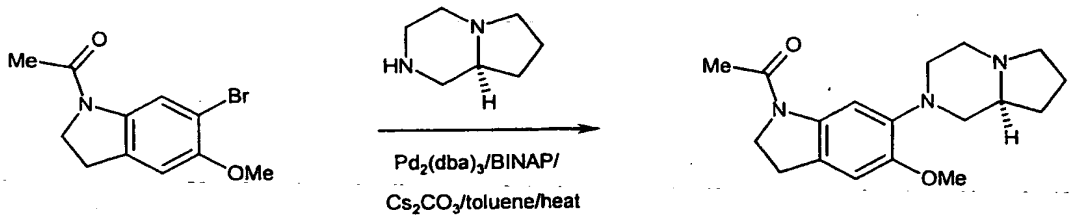
Scheme 2




i) EtOCOCl/THF/4-methylmorpholine;
ii) CF3COOH/CH2Cl2;
iii) BrCH2COBr/iPr2EtN;
iv) NaH/DMF;
v) H2/Pd
vi) BH3:THF.

Alternatively, intermediate compounds of formula (III) and (V) or protected derivatives thereof can be synthesised by the palladium catalysed amination of aryl halides by methodology similar to that described by Wolfe and Buchwald (J. Org. Chem., 1997, 62, 6066). It will be recognised by those skilled in the art that certain changes or modifications to such methodology may be necessary in order to improve reaction yields. By way of illustration rather than limitation, scheme 3 shows how the described methodology can be modified to provide a high yielding synthesis of an N-protected azabicylic indoline derivative.

Scheme 3




It will be further appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques can be used. For example, primary amines can be protected as phthalimide, benzyl, t-butyloxy carbonyl, benzyloxycarbonyl or trityl derivatives. These groups can be removed by conventional procedures well known in the art.

Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection is achieved using standard conditions.

The involvement of serotonin receptors in a number of pharmacological effects has been reviewed by R. A. Glennon in "Serotonin Receptors: Clinical Implications", Neuroscience and Behavioural Reviews, 1990, 14, 35 and by L.O.Wilkinson and C.T. Dourish in "Serotonin Receptor Subtypes : Basic and Clinical Aspects" S. Peroutka Ed., John Wiley and Sons, New York, 1991 p.147.

Serotonin (5-hydroxytryptamine; 5HT) receptors have been implicated in a number of pharmacological effects including mood disorders including depression, seasonal affective disorder and dysthymia, anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnesic disorders and age-associated memory impairment; disorders of eating behaviours, including anorexia nervosa and bulimia nervosa, sleep disorders (including disturbances of Circadian rhythm), motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders. Serotonin receptor ligands have been shown to be of use in the treatment of emesis and nausea and may also be of use in endocrine disorders such as hyperlactinaemia, vasospasm (particularly in the cerebral vasculature), cerebellar ataxia and hypertension, as well as disorders of the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction and hypothermia.

Ligands with high affinity for the $5HT_1$ receptors are well recognised as having therapeutic utility for the treatment of the above conditions. For example: WO 95/31988 refers to the use of a 5-$HT_{1D}$ receptor antagonist in conjunction with a 5-$HT_{1A}$ receptor antagonist to treat CNS, endocrine and GI disorders; K. Rasmussen (Annual Reports in Medicinal Chemistry, (1995) 30, 1) describes the utility of 5-$HT_{1A}$ receptor agonists and partial agonists in the treatment of various CNS disorders; P. Trouillas (Progress in Brain Research, C.I. de Zeeuw, P. Stara and J. Voogd, Eds. 1997, 144, 589) and G. Maura (J. Neurochemistry, 1996, 66, 202) propose that administration of agonist ligands selective for the 5-$HT_{1A}$ receptor or for both 5-$HT_{1A}$ and 5-$HT_{1D}$ receptors should provide effective treatment for human cerebellar ataxias.

The present invention also provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

In a further aspect the invention provides a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such treatment of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof.

In particular the invention provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

The affinities of the compounds of this invention for the $5HT_{1A}$, $5\text{-}HT_{1B}$ and $5\text{-}HT_{1D}$ receptors can be determined by the following radioligand binding assay. HEK 293 cells expressing $5\text{-}HT_{1A}$ receptors ($4 \times 10^7$/ml) are homogenised in Tris buffer and stored in 1 ml aliquots. CHO cells expressing $5\text{-}HT_{1B}$ receptors ($4 \times 10^7$ cells/ml) are homogenised in Tris buffer and stored in 1.5 ml aliquots. CHO cells expressing $5\text{-}HT_{1D}$ receptors ($0.563 \times 10^8$/ml) are homogenised in Tris buffer and stored in 1 ml aliquots. 0.4 ml of a cell suspension is incubated with [$^3$H]-5-HT (4 nM) for $5\text{-}HT_{1B/1D}$ receptors and [$^3$H]-8-OH DPAT (1 nM) for $5\text{-}HT_{1A}$ receptors in Tris Mg HCl buffer (pH 7.7) and test drug, at 37°C for 45 minutes. Each test drug is tested at 10 concentrations (0.01 mM to 0.3 nM final concentration), with non-specific binding defined using 0.01 mM 5-HT. The total assay volume is 0.5 ml. Incubation is stopped by rapid filtration using a Packard Filtermate (filters pre-soaked in 0.3% polyethylenimine) and radioactivity measured by Topcount scintillation counting. pKi values are calculated from the $IC_{50}$ generated by an iterative least squares curve fitting programme.

The intrinsic activity of the compounds of this invention can be determined according to the following procedure. HEK293 cell membranes stably expressing human $5\text{-}HT_{1A}$ receptors and CHO cell membranes stably expressing human $5\text{-}HT_{1B}$ receptors are homogenised in HEPES/EDTA buffer and stored in 1 ml aliquots, and [$^{35}$S]GTPγS binding studies are carried out essentially as described by Lazareno *et al.*, (Life Sci., 1993, **52**, 449) with some minor modifications. Membranes from $10^6$ cells are pre-incubated at 30°C for 30 min in 20 mM HEPES buffer (pH 7.4) in the presence of $MgCl_2$ (3 mM), NaCl (100 mM), GDP (10 μM) and ascorbate (0.2 mM), with or without compounds. The reaction is started by the addition of 10 μl of [$^{35}$S]GTPγS (100 pM, assay concentration) followed by a further 30 minutes incubation at 30°C. Non-specific binding was determined using non-radiolabelled GTPγS (20 μM) added prior to the membranes. The reaction is terminated by rapid filtration through Whatman GF/B grade filters followed by 5 x 1 ml washes with ice cold HEPES (20 mM) /$MgCl_2$ (3 mM) buffer. Radioactivity is measured using liquid scintillation spectrometry. This procedure is hereafter referred to as the [$^{35}$S]GTPγS functional assay.

The compounds of formula (I) show high affinity for the $5HT_{1A}$, $5\text{-}HT_{1B}$ and $5\text{-}HT_{1D}$ receptors. It has been found, using the [$^{35}$S]GTPγS functional assay, that certain compounds of formula (I) show varying levels of intrinsic efficacy, which is defined by a scale ranging from 1.0 to 0 (1 defines the maximum response elicited by the agonist 5-HT, 0 defines zero intrinsic efficacy). The difficulties in describing intrinsic activity of drugs acting at G protein coupled receptors is recognised in the art (Hoyer and Boddeke, Trends in Pharmacological Sciences, July 1993, [Vol. 14], page 270-275). We believe that however these ligands are classified according to this functional assay, the compounds of this invention will be useful antidepressants *in vivo*. It is believed that the preferred compounds of this invention will display $5HT_{1A}$, $5\text{-}HT_{1B}$ and $5\text{-}HT_{1D}$ antagonist activity *in vivo* and that such compounds will have a rapid onset of action. A rapid onset of action is particularly advantageous for antidepressant compounds: by 'rapid onset of action' we mean that a therapeutic response is seen within 7 days from first administration of the compound, as opposed to a period of about 21 days or more which is typical of SSRI's, tricyclic antidepressants and buspirone.

Compounds of formula (I) which have an intrinsic activity of 0.5 or less in the [$^{35}$S]GTPγS functional assay are particularly preferred, as these compounds are more likely to be full antagonists *in vivo*. As disclosed in WO 95/31988, the simultaneous antagonism of pre-synaptic $5HT_{1A/1B/1D}$ receptors will result in increased release of 5HT *in vivo* and this will improve 5HT neurotransmission.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, a selective serotonin reuptake inhibitor (SSRI) antidepressant.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants,

disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Examples illustrate the preparation of compounds of the invention.

**Description 1**

**4-(Pyridin-4-yl)naphth-1-ylamine (D1)**

A stirred suspension of 4-bromonaphth-1-ylamine (10 g, 45 mmole) in 1,2-dimethoxyethane (400 ml) and water (100 ml) containing $Na_2CO_3$ (14 g) was flushed with argon for 20 minutes. Tetrakis(triphenylphosphine)palladium (0) (2.75 g, 2.4 mmole) was added followed by pyridin-4-ylboronic acid (5.7 g, 46 mmole) and the

mixture heated at reflux for 5 hours. The mixture was concentrated *in vacuo* to a brown slurry and partitioned between DCM and water. The aqueous was further extracted with DCM and the combined organics dried ($Na_2SO_4$) and concentrated *in vacuo* to a brown solid (13.2 g). Purification of the solid by flash chromatography eluting with EtOAc afforded the title compound as a yellow crystalline solid (7.8 g, 78%).
$^1H$ NMR (250MHz, $CDCl_3$) δ (ppm): 8.68 (d, 2H), 7.90 (d, 2H), 7.30 (m, 5H), 6.84 (d, 1H), 4.32 (s, 2H).

**Description 2**

**N-[2-Methoxy-5-nitrophenyl]-(S)-1-(tert-butoxycarbonyl)pyrrolidin-2-ylcarboxamide (D2)**

Ethyl chloroformate (1.3 ml, 14 mmole) was added dropwise to a solution of (S)-1-(tert-butoxycarbonyl)pyrrolidin-2-ylcarboxylic acid (3.0 g, 14 mmole) and 4-methylmorpholine (1.5 ml, 14 mmole) in THF (30 ml) at -10°C. The resulting mixture was stirred at -10°C for 10 minutes, then 2-methoxy-5-nitroaniline (EP 0533267A1) (2.35 g, 14 mmole) was added. The mixture was stirred at -10°C for 30 minutes and then at room temperature for 17 hours. The precipitate was removed by filtration and washed with THF (3 x 20 ml). The filtrate and washings were combined and evaporated to dryness. The residue was dissolved in DCM (100 ml), washed with aqueous $NaHCO_3$ solution (2 x 30 ml), dried ($Na_2SO_4$), and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with DCM-EtOAc gradient to give the title compound as a colourless glass (3.81 g, 75%). MS: m/z (MNa+) = 389.

**Description 3**

**N-[2-Methoxy-5-nitrophenyl]-(S)-pyrrolidin-2-ylcarboxamide (D3)**

A solution N-[2-methoxy-5-nitrophenyl]-(S)-1-(tert-butoxycarbonyl)pyrrolidin-2-ylcarboxamide (D2, 1.8 g, 4.9 mmole), trifluoroacetic acid (2.65 ml) and water (0.1 ml) in DCM (15 ml) was stirred at room temperature for 17 hours. The solvents were removed *in vacuo* and the residue was co-evaporated with toluene (2 x 40 ml). The resulting solid was dissolved in DCM (200 ml) and washed with aqueous $NaHCO_3$ solution (2 x 50 ml). The aqueous layer was extracted with DCM (4 x 50 ml), and the combined extracts were dried ($Na_2SO_4$) and concentrated *in vacuo* to give the title compound as a cream solid (1.01 g, 77%). MS: m/z (MH) = 266.

**Description 4**

**N-[2-Methoxy-5-nitrophenyl]-(S)-1-(bromoacetyl)pyrrolidin-2-ylcarb xamide (D4)**

A stirred solution of N-[2-methoxy-5-nitrophenyl]-(S)-pyrrolidin-2-ylcarboxamide (D3, 0.2 g, 0.75 mmole) and N,N-diisopropylethylamine (0.13 ml, 0.75 mmole) in DCM (10 ml) at -10°C was treated dropwise with bromoacetyl bromide (0.75 mmole, 0.07 ml) in DCM (1 ml). The resulting mixture was stirred at -10°C for 30 minutes, then at room temperature for 20 minutes. It was diluted with DCM (50 ml), washed with aqueous $NaHCO_3$ solution (1 x 20 ml), water (1 x 20 ml) and dried ($Na_2SO_4$). The solvent was removed *in vacuo* and the residue was co-evaporated with toluene (2 x 20 ml) to give the title compound (0.29 g), which was used without purification in the next step.
MS: m/z (MH) = 387.

**Description 5**

**(S)-2-(2-Methoxy-5-nitrophenyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (D5)**

A mixture of N-[2-methoxy-5-nitrophenyl]-(S)-1-(bromoacetyl)pyrrolidin-2-ylcarboxamide (D4, 0.28 g, 0.7 mmole) and NaH (50 mg, 60% dispersion in mineral oil) in DMF (5 ml) was stirred at room temperature for 2 hours. Additional NaH was then added and the mixture was stirred at room temperature for 17 hours. The precipitate was filtered off and washed with DCM (60 ml). The filtrate and washings were combined and evaporated to dryness. The residue was co-evaporated with toluene (2 x 10 ml). The residue was purified by column chromatography on silica gel eluting with DCM-MeOH gradient to give the title compound as a colourless solid (79 mg, 34% after two steps).
MS: m/z (MH) = 306.

**Description 6**

**(S)-2-(5-Amino-2-methoxyphenyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (D6)**

A mixture of (S)-2-(2-methoxy-5-nitrophenyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (D5, 70 mg) and Pd/C (80 mg) in EtOH:EtOAc (8:2, 40 ml) was stirred at room temperature under an atmosphere of hydrogen for 7.5 hours. The catalyst was filtered off, washed with EtOH (3 x 15 ml) and EtOAc (1 x 15 ml). The filtrate and washings were combined and evaporated to dryness. The residue was purified by column chromatography eluting with DCM-MeOH gradient to give the title compound as a colourless solid (56 mg, 89%). MS: m/z (MH) = 276.

**Description 7**

**(S)-4-Methoxy-3-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)aniline (D7)**

A solution of (S)-2-(5-amino-2-methoxyphenyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (D6, 55 mg, 0.2 mmole) and borane-THF complex (1M solution in THF, 1.2 ml) in THF (5 ml) was heated under reflux for 5 hours. A further amount of borane-THF

complex (1M solution, 0.6 ml) was then added and the reaction was heated under reflux for another 2 hours. The solution was diluted with dry MeOH (5 ml) and the solvents were removed. The residue was co-evaporated with dry benzene (2 x 5 ml) and redissolved in dry MeOH (5 ml). Cesium fluoride (120 mg, 0.8 mmole) and dry $K_2CO_3$ (120 mg, 0.87 mmole) were added and the mixture was heated under reflux for 17 hours. Additional MeOH (5 ml), cesium fluoride (120 mg, 0.8 mmole) and dry $K_2CO_3$ (120 mg, 0.87 mmole) were added and reflux was continued for 6 hours, when further cesium fluoride (60 mg, 0.4 mmole) and dry $K_2CO_3$ (60 mg, 0.43 mmole) were added and reflux continued for 3 hours. The solvent was removed *in vacuo*, the residue was treated with DCM (50 ml), washed with brine (3 x 20 ml), water (1 x 10 ml) and dried ($Na_2SO_4$). The solvent was removed *in vacuo* to give the title compound as a tan gum (42 mg, 85%). $^1$H NMR (250MHz, $CDCl_3$) δ (ppm): 6.68 (d, 1H), 6.38 (d, 1H), 6.32 (dd, 1H), 3.79 (s, 3H), 3.62-3.28 (m, 2H + br s, 2H), 3.19-3.05 (m, 2H), 2.87-2.73 (m, 1H), 2.56-2.40 (m, 2H), 2.35-2.15 (m, 2H), 1.96-1.65 (m, 3H), 1.58-1.40 (m, 1H). MS: m/z (MH) = 248.

**Description 8**

**5-Carboxynaphth-1-ylboronic acid (D8)**

A stirred solution of 5-bromo-1-naphthoic acid (Bull. Soc. Chim. Fr., 1968, 7, 2957) (22.3 g, 0.089 mole) in dry THF (1000 ml) at -60°C under argon was treated dropwise over 15 minutes with 1.6M n-butyllithium in hexane (125 ml, 0.20 mole). The initial brown solution gave a beige precipitate as the first equivalent was added, which re-dissolved on addition of the second equivalent. The resulting solution was stirred at -60°C for 40 minutes, then triisopropylborate (51 ml, 0.22 mole) was added, and the mixture stirred at -60°C for a further 1 hour, before warming gradually to -10°C. Saturated aqueous $NH_4Cl$ solution (300 ml) was added, followed by water (400 ml) and then 5M HCl solution (200 ml). The resulting mixture was concentrated *in vacuo* to approximately 1000 ml volume, then basified by addition of 40% NaOH solution and washed with EtOAc. The aqueous was added to excess 5M HCl solution and the solid which precipitated out was filtered off, washed with water and dried to afford a white solid (9.67 g), which contained approx. 50% of the title compound together with 1-naphthoic acid.

**Description 9**

**5-(6-Methylpyridin-2-yl)-1-naphthoic acid (D9)**

The title compound was prepared from 2-bromo-6-methylpyridine and 5-carboxynaphth-1-ylboronic acid (D8) using a similar procedure to Description 1 as beige solid (46%).

$^1$H NMR (250MHz, d$^6$DMSO) δ (ppm): 8.90 (d, 1H), 8.13 (d, 1H), 8.06 (dd, 1H), 7.84 (t, 1H), 7.67 (t, 1H), 7.62-7.46 (m, 2H), 7.41 (d, 1H), 7.32 (d, 1H), 2.55 (s, 3H). Acid proton not observed.

**Description 10**

**5-(2-Methylpyridin-3-yl)-1-naphthoic acid (D10)**

The title compound was prepared from 2-methyl-3-iodopyridine and 5-carboxynaphth-1-ylboronic acid (D8) using a similar procedure to Description 1 as a beige solid (61%).
$^1$H NMR (250MHz, d$^6$DMSO) δ (ppm): 13.3 (br s, 1H), 8.91 (d, 1H), 8.59 (dd, 1H), 8.15 (dd, 1H), 7.78-7.69 (m, 1H), 7.64 (dd, 1H), 7.60-7.45 (m, 3H), 7.43-7.35 (m, 1H), 2.13 (s, 3H).

**Description 11**

**2,6-Dimethyl-4-iodopyridine (D11)**

A stirred solution of 4-chloro-2,6-dimethylpyridine (Chem. Abs. 1952, **46**, 4541) (2.6 g, 18 mmole) in 2-butanone (250 ml) was treated with sodium iodide (17.6 g, 120 mmole) and 4-toluenesulphonic acid (3.4 g, 18 mmole) and the mixture heated at reflux under argon for 72 hours. The reaction mixture was cooled, then concentrated *in vacuo* and the residue was treated with water (200 ml) and extracted with EtOAc. The extract was washed with aqueous sodium thiosulphate solution, then dried ($Na_2SO_4$) and concentrated *in vacuo* to afford the title compound as a white solid, which was converted to its hydrochloride salt as a white solid from acetone (3.44 g, 69%).
$^1$H NMR (free base) (250 MHz, $CDCl_3$) δ (ppm): 7.37 (s, 2H), 2.46 (s, 6H).
MS: m/z (MH) = 234.

**Description 12**

**5-(2,6-Dimethylpyridin-4-yl)-1-naphthoic acid (D12)**

The title compound was prepared from 2,6-dimethyl-4-iodopyridine (D11) and 5-carboxynaphth-1-ylboronic acid (D8) using a similar procedure to Description 1 as a white solid (70%).
$^1$H NMR (250 MHz, d$^6$DMSO) δ (ppm): 8.75 (d, 1H), 7.99 (dd, 1H), 7.80 (d, 1H), 7.60-7.52 (m, 1H), 7.50-7.32 (m, 2H), 7.00 (s, 2H), 2.36 (s, 6H). Acid proton not observed.

**Description 13**

**3-Bromo-2,6-dimethylpyridine (D13)**

A stirred solution of phosphorus oxybromide (25 g, 0.085 mole) in 1,2-dichloroethane (250 ml) at room temperature under argon was treated with 2,6-lutidine-N-oxide (10 g,

0.081 mole), then heated at reflux for 6 hours. The mixture was allowed to cool, then poured slowly into well stirred ice/water (400 ml) and basified by addition of solid $K_2CO_3$. The aqueous mixture was extracted with DCM and the extract dried ($Na_2SO_4$) and concentrated under vacuum. The residue was chromatographed on silica gel eluting with 1:1 ether /60-80 petrol to separate four components.
The second component was 3-bromo-2,6-dimethylpyridine (2.5 g, 21%) as a yellow oil; $^1$H NMR (250MHz, $CDCl_3$) δ (ppm): 7.66 (d, 1H), 6.86 (d, 1H), 2.63 (s, 3H), 2.48 (s, 3H) and the third component was 4-bromo-2,6-dimethylpyridine (1.5 g, 12%) as a pale yellow oil; $^1$H NMR (250MHz, $CDCl_3$) δ (ppm): 7.16 (s, 2H), 2.50 (s, 6H).

**Description 14**

**5-(2,6-Dimethylpyridin-3-yl)-1-naphthoic acid (D14)**

The title compound was prepared from 2,6-dimethyl-3-bromopyridine (D13) and 5-carboxynaphth-1-ylboronic acid (D8) using a similar procedure to Description 1 as a white solid (70%).

**Description 15**

**1-Acetyl-6-bromo-5-methoxyindoline (D15)**

A stirred solution of 1-acetyl-6-bromo-5-hydroxyindoline (Tetrahedron, 1973, 29(8), 1115) (5.0 g, 19.5 mmole) in DMF (100 ml) under argon was treated with $K_2CO_3$ (7.7 g, 55.8 mmole) and after 30 minutes with MeI (5.7 g, 40 mmole). After 15 hours the mixture was diluted with water (200 ml) and extracted with EtOAc (3 x 100 ml). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated to dryness *in vacuo* giving the title compound as a white crystalline solid (4.6 g, 87%).
$^1$H NMR (250 MHz, d$^6$DMSO) δ (ppm): 8.22 (s, 1H), 7.06 (s, 1H), 4.09 (t, 2H), 3.80 (s, 3H), 3.11 (t, 2H), 2.12 (s, 3H). MS: m/z (MH) = 270, 272.

**Description 16**

**(S)-(-)-1-Acetyl-5-methoxy-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D16)**

Dipalladium tris(dibenzylideneacetone) (17 mg, 18.5 μmole), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (40 mg, 59.5 μmole) and caesium carbonate (167 mg, 513 μmole) were placed in a flask which was pump-filled repeatedly with argon. Toluene (5 ml) was added, and the flask sonicated for 10 minutes. A suspension of 1-acetyl-6-bromo-5-methoxyindoline (D15, 100 mg, 370 μmole) in toluene (5 ml) was added, followed by (S)-(-)-octahydropyrrolo[1,2-*a*]pyrazine (*J. Med. Chem.* 1993, 36, 2311) (140 mg, 1.1 mmole), both by syringe. The suspension was stirred vigorously and

heated under reflux. After 18 hours the suspension was cooled to 0°C, diluted with DCM (10 ml) and extracted with 2M HCl solution (3 x 20 ml). The combined aqueous layers were brought to pH 10 with solid $K_2CO_3$ at 0°C, and extracted with DCM (3 x 50 ml). The combined organic phases were dried ($MgSO_4$), filtered and concentrated to dryness *in vacuo* giving the title compound as a pale brown crystalline solid (76 mg, 65%).
$^1H$ NMR (250 MHz, $CDCl_3$) δ (ppm): 8.01 (s, 1H), 6.70 (s, 1H), 4.02 (d, 2H), 3.83 (s, 3H), 3.51 (br t, 2H), 3.16-3.06 (m, 4H), 2.82 (td, 1H), 2.60-2.45 (m, 2H), 2.31-2.20 (m, 2H), 2.18 (s, 3H), 1.90-1.70 (m, 3H), 1.52-1.40 (m, 1H). MS: m/z (MH) = 316.

**Description 17**
**(S)-(-)-5-Methoxy-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D17)**
A stirred solution of (S)-(-)-1-acetyl-5-methoxy-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D16, 101 mg, 321 μmole) in 2M HCl solution (4 ml) was heated under reflux for 2 hours. After cooling to 0°C, the solution was brought to pH 10 with solid $K_2CO_3$ and extracted with DCM (3 x 10 ml). The combined organic phases were dried ($Na_2SO_4$), filtered and concentrated to dryness *in vacuo* giving the title compound as a brown oil (70 mg, 80%).
$^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 6.72 (s, 1H), 6.42 (s, 1H), 3.79 (s, 3H), 3.52 (t, 2H), 3.51-3.48 (m, 1H), 3.41 (br d, 1H), 3.11-3.07 (m, 2H), 2.98 (t, 2H), 2.77 (td, 1H), 2.48 (td, 1H), 2.44 (t, 1H), 2.30-2.22 (m, 1H), 2.20 (q, 1H), 1.92-1.80 (m, 2H), 1.80-1.70 (m, 1H), 1.51-1.40 (m, 1H). NH signal not observed. MS: m/z (MH) = 274.

**Description 18**
**(R)-(+)-1-Acetyl-5-methoxy-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D18)**
The title compound was prepared from 1-acetyl-6-bromo-5-methoxyindoline (D15, 100 mg, 370 μmole) and (R)-(+)-octahydropyrrolo[1,2-*a*]pyrazine (*J. Med. Chem.* 1993, 36, 2311) (140 mg, 1.1 mmole) according to Description 16, giving a brown oil which crystallized on standing (70 mg, 60%).
$^1H$ NMR (250 MHz, $CDCl_3$) δ (ppm): identical to Description 16.

**Description 19**
**(R)-(+)-5-Methoxy-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D19)**
The title compound was prepared from (R)-(+)-1-acetyl-5-methoxy-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D18, 70 mg, 222 μmole) according to the procedure of Description 17, giving a brown oil (55 mg, 91%).
$^1H$ NMR (250 MHz, $CDCl_3$) δ (ppm): identical to Description 17.

**Description 20**

**(R/S)-(+/-)-1-Acetyl-5-methoxy-6-(octahydropyrido[1,2-*a*]pyrazin-2-yl)indoline (D20)**

The title compound was prepared from 1-acetyl-6-bromo-5-methoxyindoline (D15, 200 mg, 700 μmole) and (R/S)-(+/-)-octahydropyrido[1,2-*a*]pyrazine (*J. Med. Chem.* 1993, 36, 2311) (412 mg, 2.8 mmole) according to Description 16, giving a brown oil (61 mg, 27%).

$^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.97 (s, 1H), 6.70 (s, 1H), 4.03 (t, 2H), 3.83 (s, 3H), 3.50-3.42 (m, 1H), 3.31-3.23 (m, 1H), 3.14 (t, 2H), 3.00-2.80 (m, 4H), 2.64-2.52 (m, 2H), 2.30-2.10 (m, 1H), 2.20 (s, 3H), 1.85-1.55 (m, 4H), 1.45-1.25 (m, 2H).

MS: m/z (MH) = 330.

**Description 21**

**(R/S)-(+/-)-5-Methoxy-6-(octahydropyrido[1,2-*a*]pyrazin-2-yl)indoline (D21)**

The title compound was prepared from (R/S)-(+/-)-1-acetyl-5-methoxy-6-(octahydropyrido[1,2-*a*]pyrazin-2-yl)indoline (D20, 90 mg, 270 μmole) according to Description 17, giving a brown oil (60 mg, 78%).

$^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.74 (s, 1H), 6.39 (s, 1H), 3.80 (s, 3H), 3.53 (t, 2H), 3.40-3.32 (m, 1H), 3.28-3.20 (m, 1H), 2.98 (t, 2H), 2.95-2.75 (m, 3H), 2.53 (dt, 1H), 2.42 (t, 1H), 2.25-2.05 (m, 2H), 1.85-1.50 (m, 4H), 1.40-1.22 (m, 2H). NH not discernible from spectrum. MS: m/z (MH) = 288.

**Description 22**

**1-Acetyl-6-(1,4-diazabicyclo[3.2.2]non-4-yl)-5-methoxyindoline (D22)**

The title compound was prepared from 1-acetyl-6-bromo-5-methoxyindoline (D15, 200 mg, 740 μmole) and 1,4-diazabicyclo[3.2.2]nonane (*Zh. Obsh. Khim.* 1964, 34, 2222) (280 mg, 2.2 mmole) according to Description 16, giving a brown oil which crystallized on standing (51 mg, 22%).

$^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.03 (s, 1H), 6.72 (s, 1H), 4.05 (t, 2H), 3.82 (s, 3H), 3.67 (m, 1H), 3.42 (m, 4H), 3.29 (t, 4H), 3.16 (t, 2H), 2.28 (m, 2H), 2.21 (s, 3H), 1.84 (m, 2H). MS: m/z (MH) = 316.

**Description 23**

**6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-5-methoxyindoline (D23)**

The title compound was prepared from 1-acetyl-6-(1,4-diazabicyclo[3.2.2]non-4-yl)-5-methoxyindoline (D22, 51 mg, 163 μmole) according to Description 17, giving a brown oil (35 mg, 79%).

$^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 6.71 (s, 1H), 6.45 (s, 1H), 3.78 (s, 3H), 3.53 (m, 1 H), 3.52 (t, 2H), 3.20 (m, 4H), 3.01 (m, 4H), 2.98 (t, 2H), 2.10 (m, 2H), 1.61 (m, 2H). NH signal not observed. MS: m/z (MH) = 274.

**Description 24**

**1-Benzyl-6-nitroindoline (D24)**

To a stirred solution of 6-nitroindoline (25.0 g, 152 mmole) in acetone (500 ml) under argon was added $K_2CO_3$ (23.5 g, 170 mmole) followed by benzyl bromide (28.7 g, 170 mmole). After 24 hours a further portion of benzyl bromide (7 g, 40 mmole) was added and the mixture stirred for 24 hours. The mixture was filtered and the residue washed with acetone. The combined filtrate and washings were evaporated to dryness *in vacuo* and the residue partitioned between DCM and dilute aqueous $K_2CO_3$ solution. The organic phase was dried ($Na_2SO_4$) and evaporated to dryness *in vacuo* affording the title compound, which was then washed with hexane and dried *in vacuo* at 40°C (36.0 g, 93%).

$^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.53 (dd, 1H), 7.40-7.27 (m, 5H), 7.26 (d, 1H), 7.11 (d, 1H), 4.34 (s, 2H), 3.47 (t, 2H), 3.05 (t, 2H).

**Description 25**

**6-Amino-1-benzylindoline (D25)**

A stirred solution of 1-benzyl-6-nitroindoline (D24, 33.4 g, 130 mmole) in EtOH (650 ml) under argon was treated dropwise over 40 minutes with a solution of $SnCl_2.2H_2O$ (96.8 g, 429 mmole) in conc. HCl (130 ml). The mixture was stirred until all material had dissolved, then left to stand at room temperature for 48 hours. The mixture was concentrated *in vacuo* and the residue diluted with water, basified with $K_2CO_3$ and extracted with DCM. The organic phase was washed with water, dried ($Na_2SO_4$) and concentrated to dryness *in vacuo* to afford the title compound (30.0 g, 100%).

$^1$H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.36-7.17 (m, 5H), 6.84 (d, 1H), 5.99 (dd, 1H), 5.87 (d, 1H), 4.19 (s, 2H), 3.47 (s, 2H), 3.27 (t, 2H), 2.84 (t, 2H). MS: m/z (MH) = 225.

**Description 26**

**N-[1-Benzylindolin-6-yl]-(S)-1-(tert-butoxycarbonyl)pyrrolidin-2-ylcarboxamide (D26)**

To a stirred solution of (S)-1-(tert-butoxycarbonyl)pyrrolidin-2-ylcarboxylic acid (28.8 g, 130 mmole) in DCM (500 ml) under argon were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (28.6 g, 150 mmole) and 1-hydroxybenzotriazole (20.2 g, 150 mmole). After 30 minutes, a solution of 6-amino-1-benzylindoline (D25, 30.0 g,

130 mmole) in DCM (500 ml) was added and the mixture stirred at room temperature for 24 hours. The mixture was washed with water and dilute aqueous $NaHCO_3$ solution, dried ($Na_2SO_4$) and concentrated to dryness *in vacuo*. Purification by chromatography on neutral alumina, eluting with DCM-$Et_2O$ gradient, afforded the title compound (26.1 g, 46%).

$^1H$ NMR (250 MHz, $CDCl_3$) δ (ppm): 9.28 (br s, 1H), 7.34-7.23 (m, 5H), 7.00-6.93 (m, 2H), 6.66 (d, 1H), 4.42 (br s, 1H), 4.25 (s, 2H), 3.50-3.26 (br m, 2H + t, 2H), 2.91 (t, 2H), 2.50 (br s, 1H), 2.21 (br s, 1H), 1.91 (br m, 2H), 1.46 (s, 9H). MS: m/z ($MNa^+$) = 444.

**Description 27**

**N-[1-Benzylindolin-6-yl]-(S)-pyrrolidin-2-ylcarboxamide (D27)**

The title compound was prepared from N-[1-benzylindolin-6-yl]-(S)-1-(tert-butoxycarbonyl)pyrrolidin-2-ylcarboxamide (D26) using a similar procedure to Description 3 (92%).

$^1H$ NMR (250 MHz, $CDCl_3$) δ (ppm): 9.60 (s, 1H), 7.36-7.22 (m, 5H), 7.02-6.98 (m, 2H), 6.75 (dd, 1H), 4.27 (s, 2H), 3.81 (dd, 1H), 3.29 (t, 2H), 3.10-2.87 (m, 4H), 2.26-1.95 (m, 3H), 1.81-1.64 (m, 2H). MS: m/z (MH) = 322.

**Description 28**

**N-[1-Benzylindolin-6-yl]-(S)-1-(chloroacetyl)pyrrolidin-2-ylcarboxamide (D28)**

The title compound was prepared from N-[1-benzylindolin-6-yl]-(S)-pyrrolidin-2-ylcarboxamide (D27) and chloroacetyl chloride using a similar procedure to Description 4. MS: m/z (MH) = 398.

**Description 29**

**(S)-(-)-2-(1-Benzylindolin-6-yl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (D29)**

To a stirred solution of N-[1-benzylindolin-6-yl]-(S)-1-(chloroacetyl)pyrrolidin-2-ylcarboxamide (D28 , 24.7 g, 62.1 mmole) in DMF (700 ml) under argon was added a solution of $KO^tBu$ (13.8 g, 123 mmole) in DMF (40 ml), over 45 min. After 1 hour, the mixture was adjusted to pH 8 by the dropwise addition of conc. HCl, and the DMF was removed *in vacuo*. The residue was partitioned between EtOAc and water and the organic phase was separated, dried ($Na_2SO_4$) and concentrated to dryness *in vacuo*. Purification by silica gel chromatography, eluting with EtOAc, afforded the title compound (8.59 g, 38%).

$^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36-7.24 (m, 5H), 7.06 (d, 1H), 6.48 (dd, 1H), 6.36 (d, 1H), 4.48 (br d, 1H), 4.24-4.20 (m, 3H), 4.11 (br d, 1H), 3.71-3.58 (m, 2H), 3.35

(t, 2H), 2.96 (t, 2H), 2.46-2.30 (m, 1H), 2.27-2.17 (m, 1H), 2.10-2.04 (m, 1H), 1.99-1.90 (m, 1H). MS: m/z (MH) = 362.

**Descripti n 30**

**(S)-(-)-1-Benzyl-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D30)**

A stirred solution of $NaBH_4$ (5.42 g, 143 mmole) in anhydrous THF (700 ml) under argon was cooled to 0°C and treated with boron trifluoride etherate (17.7 ml). After 3 hours at room temperature a solution of (S)-(-)-2-(1-benzylindolin-6-yl)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (D29, 8.59 g, 23.8 mmole) in anhydrous THF (300 ml) was added and the mixture heated at reflux for 3 hours. The THF was removed *in vacuo* and the residue treated with EtOH (500 ml) and 5M HCl solution (500 ml) and heated at reflux for 2 hours. The EtOH was removed *in vacuo* and the residue basified with 10% aqueous $K_2CO_3$ solution and extracted with EtOAc. The organic phase was washed with water, dried ($Na_2SO_4$) and concentrated to dryness *in vacuo*. Purification by silica gel chromatography, eluting with DCM-MeOH gradient, afforded the title compound (7.92 g, 100%).

$^1H$ NMR (250 MHz, $CDCl_3$) δ (ppm): 7.38-7.28 (m, 5H), 6.97 (d, 1H), 6.26 (dd, 1H), 6.18 (d, 1H), 4.25 (s, 2H), 3.68 (t, 2H), 3.58 (t, 2H), 3.29 (t, 2H), 3.17-3.09 (m, 2H), 2.96-2.84 (m, 3H), 2.54 (br t, 1H), 2.41 (dt, 1H), 1.95-1.68 (m, 3H), 1.56-1.49 (m, 1H). MS: m/z (MH) = 334.

**Description 31**

**(S)-(-)-6-(Octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D31)**

(S)-(-)-1-Benzyl-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D30, 1.0 g, 3.0 mmole) in EtOH (40 ml) and conc. HCl acid (10 ml) was hydrogenated over 10% palladium on charcoal at 50 psi (344.8kPa) and room temperature for 3 hours. The mixture was then filtered through kieselguhr and concentrated *in vacuo*. The residue was partitioned between DCM and 10% aqueous $K_2CO_3$ solution and the organic phase separated, dried ($Na_2SO_4$) and concentrated to *in vacuo*. Purification by silica gel chromatography eluting with DCM-MeOH gradient afforded the title compound (368 mg, 50%).

$^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 6.98 (dd, 1H), 6.33-6.31 (m, 2H), 3.68-3.51 (m, 5H), 3.15-3.09 (m, 2H), 2.94 (t, 2H), 2.88 (dt, 1H), 2.50 (dd, 1H), 2.38 (dt, 1H), 2.20-2.12 (m, 2H), 1.90-1.68 (m, 3H), 1.51-1.43 (m, 1H). MS: m/z (MH) = 244.

**Descripti n 32**

**(S)-(-)-1-Acetyl-6-(octahydr pyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D32)**

A solution of (S)-(-)-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D31, 2.83 g, 11.6 mmole) in DCM (30 ml) was treated with acetic anhydride (1.21 ml, 12.8 mmole) and stirred at room temperature for 4 hours. Dilute aqueous $Na_2CO_3$ solution was added and the mixture stirred vigorously for 20 minutes, then the organic phase was separated, dried ($MgSO_4$) and concentrated to dryness *in vacuo* affording the title compound as a brown solid (2.93 g, 88%).

$^1H$ NMR (250 MHz, $CDCl_3$) δ (ppm): 8.00 (d, 1H), 7.03 (d, 1H), 6.60 (dd, 1H), 4.04 (t, 2H), 3.77 (br d, 1H), 3.65-3.57 (m, 1H), 3.14-3.07 (m, 4H), 2.90 (dt, 1H), 2.53 (t, 1H), 2.37 (dt, 1H), 2.22 (s, 3H), 2.22-2.12 (m, 2H), 1.92-1.76 (m, 3H), 1.51-1.44 (m, 1H). MS: m/z (MH) = 286.

**Description 33**

**(S)-(-)-1-Acetyl-5-chloro-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D33)**

To a stirred solution of (S)-(-)-1-acetyl-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D32, 1.00 g, 3.5 mmole) in glacial AcOH (15 ml) was added N-chlorosuccinimide (0.56 g, 4.2 mmole). After 6 hours at room temperature, water (20 ml) was added and the pH of the mixture adjusted to pH 10 with $K_2CO_3$. The aqueous was extracted with DCM and the organic phase separated, dried ($MgSO_4$) and concentrated to dryness *in vacuo* affording the title compound as a dark brown solid (0.88 g, 79%).

$^1H$ NMR (250 MHz, $CDCl_3$) δ (ppm): 8.07 (s, 1H), 7.15 (s, 1H), 4.06 (t, 2H), 3.39 (dt, 2H), 3.13 (t, 2H), 3.16-3.09 (m, 2H), 2.89 (dt, 1H), 2.66-2.35 (m, 2H), 2.33-2.03 (m, 2H), 2.22 (s, 3H), 1.90-1.70 (m, 3H), 1.60-1.40 (m, 1H). MS: m/z (MH) = 320, 322.

**Description 34**

**(S)-(-)-5-Chloro-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D34)**

The title compound was prepared from (S)-(-)-1-acetyl-5-chloro-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D33, 880 mg, 2.75 mmole) according to the procedure of Description 17, giving a dark brown solid (502 mg, 66%).

$^1H$ NMR (250 MHz, $CDCl_3$) δ (ppm): 7.07 (s, 1H), 6.43 (s, 1H), 3.56 (t, 2H), 3.40 (td, 1H), 3.29 (dd, 1H), 3.13-3.06 (m, 2H), 2.97 (t, 2H), 2.82, (dt, 1H), 2.53-2.43 (m, 2H), 2.30-2.18 (m, 2H), 1.92-1.77 (m, 3H), 1.60-1.40 (m, 1H). MS: m/z (MH) = 278, 280.

**Description 35**

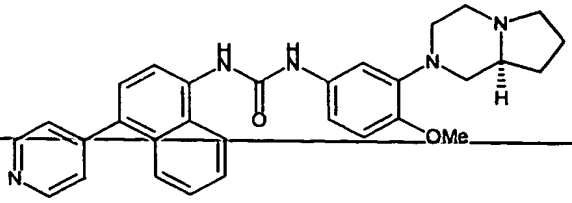
**5-(6-Methylpyridin-3-yl)-1-naphthoic acid (D35)**

The title compound was prepared from 5-bromo-2-methylpyridine and 5-carboxynaphth-1-ylboronic acid (D8) using a similar procedure to Description 1 as a beige solid (64%).

$^1$H NMR (250MHz, d$^6$DMSO) δ (ppm): 13.3 (br s, 1H), 8.90 (d, 1H), 8.53 (s, 1H), 8.15 (d, 1H), 7.93 (d, 1H), 7.83-7.67 (m, 2H), 7.62-7.47 (m, 2H), 7.43 (d, 1H), 2.57 (s, 3H).

**Example 1**

**N-[(S)-4-Methoxy-3-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)phenyl]-N'-[4-(pyridin-4-yl)naphth-1-yl]-urea (E1)**

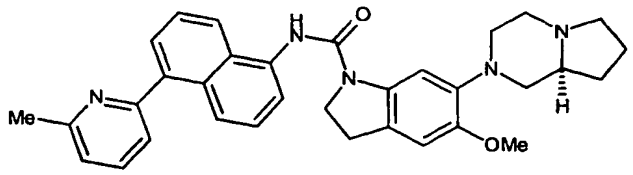


A solution of 4-(pyridin-4-yl)naphth-1-ylamine (D1, 57 mg, 0.26 mmole) and triethylamine (30 mg, 0.30 mmole) in DCM (5 ml) was added over 0.5 minutes to a stirred solution of triphosgene (27 mg, 0.09 mmole) in DCM (5 ml). The mixture was stirred at room temperatrure for 1 hour, then treated with a solution of (S)-4-methoxy-3-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)aniline (D7, 50 mg, 0.20 mmole) in DCM (5 ml), then stirred for a further 2 hours at room temperature. The mixture was washed with 10% aqueous $Na_2CO_3$ solution, dried and concentrated *in vacuo*. The residue was purified by preparative plate TLC on silica gel eluting with 15% MeOH/DCM to afford the title compound as a yellow foam (90 mg, 91%). This was converted to its hydrochloride salt as a yellow solid from acetone.

$^1$H NMR (free base) (250MHz, $CDCl_3$) δ (ppm): 8.69 (d, 2H), 7.98-7.75 (m, 3H), 7.61 (s, 1H), 7.5-7.27 (m, 6H), 7.05-6.95 (m, 2H), 6.73 (d, 1H), 3.81 (s, 3H), 3.57-3.37 (m, 2H), 3.17-3.00 (m, 2H), 2.85-2.72 (m, 1H), 2.54-2.40 (m, 2H), 2.35-2.15 (m, 2H), 1.90-1.70 (m, 3H), 1.55-1.35 (m, 1H). MS: m/z (MH) = 494.

**Example 2**

**(S)-(-)-5-Methoxy-1-[5-(6-methylpyridin-2-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (E2)**

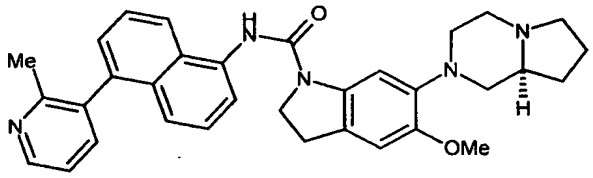


A stirred suspension of 5-(6-methylpyridin-2-yl)-1-naphthoic acid (D9, 58 mg, 220 μmole) in dry DCM (3 ml) under argon was treated with oxalyl chloride (40 μl, 300 μmole). After 3 hours the solution was concentrated to dryness, and the residue taken up into DCM (5 ml). The organic phase was washed with cold 10% aqueous $NaHCO_3$ solution (5 ml) and added dropwise to a vigorously stirred solution of sodium azide (28 mg, 430 μmole) and tetrabutylammonium iodide (5 mg, 14 μmole) in water at 0°C. After 90 minutes the organic phase was separated, washed with water (5 ml), dried ($Na_2SO_4$), filtered, diluted with toluene (5 ml) and heated under reflux for 90 min. After removing the heat source, a solution (S)-(-)-5-methoxy-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D17, 30 mg, 110 μmole) in DCM (2 ml) was added by syringe, and the new solution stirred overnight at ambient temperature. The solution was then concentrated to dryness and the residue purified by silica gel chromatography eluting with DCM/MeOH (9:1) to afford the title compound. This was dissolved in acetone, treated with a solution of HCl in dry ether (1.0 M), and concentrated to dryness *in vacuo* to give the HCl salt as a buff powder (49 mg, 78%).

$^1$H NMR (free base) (400 MHz, $CDCl_3$) δ (ppm): 7.99-7.94 (m, 1H), 7.83 (d, 1H), 7.75-7.66 (m, 3H), 7.59-7.50 (m, 2H), 7.41 (dd, 1H), 7.31 (d, 1H), 7.20 (d, 1H), 6.89 (s, 1H), 6.73 (s, 1H), 4.18 (t, 2H), 3.83 (s, 3H), 3.50 (br d, 2H), 3.20 (t, 2H), 3.14- 3.02 (m, 2H), 2.80 (td, 1H), 2.66 (s, 3H), 2.62-2.52 (m, 2H), 2.45-2.35 (m, 1H), 2.32-2.22 (m, 1H), 1.90-1.70 (m, 3H), 1.60-1.30 (m, 1H). MS: m/z (MH) = 534.

**Example 3**

**(S)-(-)-5-Methoxy-1-[5-(2-methylpyridin-3-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (E3)**



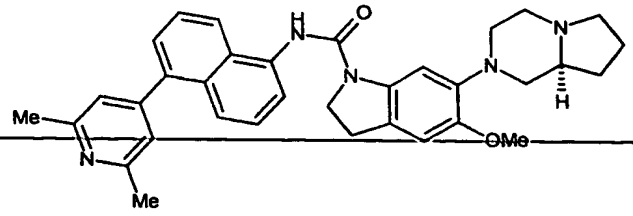

The title compound was prepared from 5-(2-methylpyridin-3-yl)-1-naphthoic acid (D10, 74 mg, 280 μmole) and (S)-(-)-5-methoxy-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D17, 35 mg, 128 μmole) according to the procedure in Example 2. The HCl salt was obtained as a pale buff powder (45 mg, 60%).

$^1$H NMR (free base) (400 MHz, $CDCl_3$) δ (ppm): 8.60 (br. d, 1H), 8.02 (d, 1H), 7.76 (m, 2H), 7.58-7.53 (m, 2H), 7.41 (t, 1H), 7.34 (d, 1H), 7.26-7.23 (m, 2H), 6.81 (s, 1H), 6.77

(s, 1H), 4.25 (t, 2H), 3.85 (s, 3H), 3.52 (br d, 2H), 3.26 (t, 2H), 3.13-3.05 (m, 2H), 2.80 (br t, 1H), 2.61-2.54 (m, 2H), 2.44-2.34 (m, 1H), 2.27 (s, 3H), 2.33-2.25 (m, 1H), 1.91-1.70 (m, 3H), 1.52-1.40 (m, 1H). MS: m/z (MH) = 534.

**Example 4**

**(S)-(-)-1-[5-(2,6-Dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-5-methoxy-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (E4)**

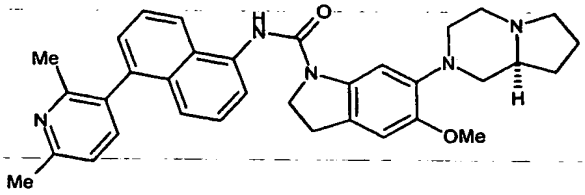



The title compound was prepared from 5-(2,6-dimethylpyridin-4-yl)-1-naphthoic acid (D12, 78 mg, 280 μmole) and (S)-(-)-5-methoxy-6-(octahydropyrrolo[1,2-a]pyrazin-2-yl)indoline (D17, 35 mg, 128 μmole) according to the procedure in Example 2. The HCl salt was obtained as a pale yellow powder (43 mg, 57%).

$^1$H NMR (free base) (400 MHz, $CDCl_3$) δ (ppm): 7.99 (d, 1H), 7.76-7.75 (m, 1H), 7.75 (s, 1H), 7.67 (d, 1H), 7.55 (dd, 1H), 7.45 (dd, 1H), 7.39 (d, 1H), 7.07 (s, 2H), 6.79 (s, 1H), 6.76 (s, 1H), 4.23 (t, 2H), 3.85 (s, 3H), 3.50 (br d, 2H), 3.25 (t, 2H), 3.12-3.03 (m, 2H), 2.79 (td, 1H), 2.61 (s, 6H), 2.57-2.50 (m, 2H), 2.39-2.30 (m, 1H), 2.29-2.20 (m, 1H), 1.90-1.70 (m, 3H), 1.50-1.40 (m, 1H). MS: m/z (MH) = 548.

**Example 5**

**(S)-(-)-1-[5-(2,6-Dimethylpyridin-3-yl)naphth-1-ylaminocarbonyl]-5-methoxy-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (E5)**

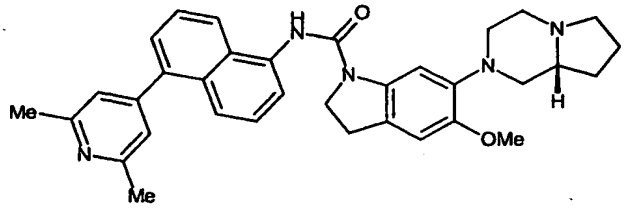



The title compound was prepared from 5-(2,6-dimethylpyridin-3-yl)-1-naphthoic acid (D14, 78 mg, 280 mmole) and (S)-(-)-5-methoxy-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D17, 35 mg, 128 μmole) according to the procedure in Example 2. The HCl salt was obtained as a pale yellow powder (49 mg, 66%).

$^1$H NMR (free base) (400 MHz, $CDCl_3$) δ (ppm): 7.99 (d, 1H), 7.76 (s, 1H), 7.73 (d, 1H), 7.55 (dd, 1H), 7.43-7.37 (m, 2H), 7.32-7.28 (m, 2H), 7.11 (d, 1H), 6.82 (s, 1H), 6.75 (s, 1H), 4.23 (t, 2H), 3.84 (s, 3H), 3.51 (br d, 2H), 3.24 (t, 2H), 3.11-3.03 (m, 2H), 2.79 (td, 1H), 2.64 (s, 3H), 2.60-2.50 (m, 2H), 2.38-2.30 (m, 1H), 2.23 (s, 3H), 2.28-2.18 (m, 1H), 1.90-1.70 (m, 3H), 1.50-1.35 (m, 1H). MS: m/z (MH) = 548.

**Example 6**

**(R)-(+)-1-[5-(2,6-Dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-5-methoxy-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (E6)**

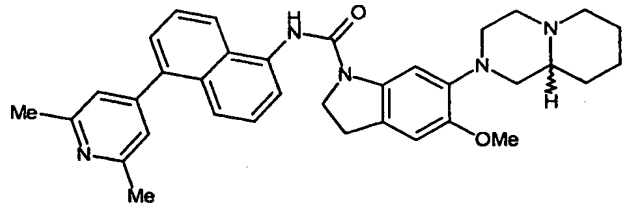



The title compound was prepared from 5-(2,6-dimethylpyridin-4-yl)-1-naphthoic acid (D12, 78 mg, 280 μmole) and (R)-(+)-6-(1,4-diazabicyclo[4.3.0]non-4-yl)-5-methoxyindoline (D19, 35 mg, 128 μmole) according to the procedure in Example 2. The HCl salt was obtained as a yellow powder (36 mg, 49%).

$^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): identical to Example 4.

**Example 7**

**(R/S)-(+/-)-1-[5-(2,6-Dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-5-methoxy-6-(octahydropyrido[1,2-*a*]pyrazin-2-yl)indoline (E7)**



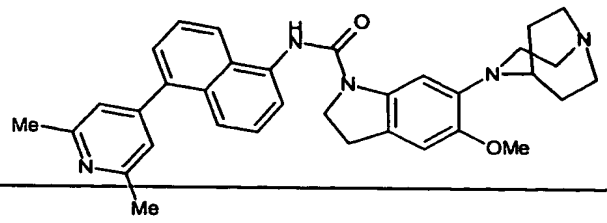

The title compound was prepared from 5-(2,6-dimethylpyridin-4-yl)-1-naphthoic acid (D12, 115mg, 400 μmole) and (R/S)-(+/-)-5-methoxy-6-(octahydropyrido[1,2-*a*]pyrazin-2-yl)indoline (D21, 60 mg, 210 μmole) according to the procedure in Example 2, as a brown foam (75 mg, 64%). The HCl salt was obtained as a yellow solid.

$^1$H NMR (HCl salt) (400 MHz, $d^6$DMSO) δ (ppm): 10.47 (br, 1H), 8.81 (s, 1H), 8.22 (d, 1H), 7.83 (br, 2H), 7.69 (m, 2H), 7.61 (m, 3H), 6.94 (s, 1H), 5.75 (s, 1H), 4.31 (t, 2H),

3.77 (s, 3H), 3.33 (m, 3H), 3.21 (m, 4H), 2.96 (m, 2H), 2.78 (s, 6H), 1.80 (m, 4H), 1.53 (m, 2H). MS: m/z (MH) = 562.

**Example 8**

**6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-1-[5-(2,6-dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-5-methoxyindoline (E8)**

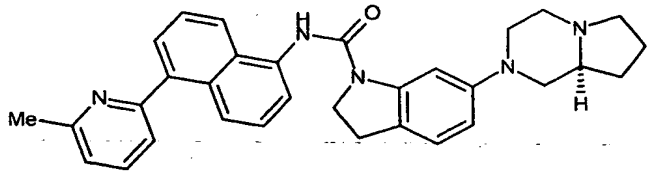



The title compound was prepared from 5-(2,6-dimethylpyridin-4-yl)-1-naphthoic acid (D12, 82 mg, 260 μmole) and 6-(1,4-diazabicyclo[3.2.2]non-4-yl)-5-methoxyindoline (D23, 35 mg, 128 μmole) according to the procedure in Example 2. The HCl salt was obtained as a brown powder (17 mg, 23%).

$^1$H NMR (free base) (400 MHz, $CDCl_3$) δ (ppm): 8.01 (d, 1H), 7.73-7.68 (m, 2H), 7.69 (s, 1H), 7.55 (dd, 1H), 7.45 (dd, 1H), 7.38 (d, 1H), 7.06 (s, 2H), 6.77 (s, 1H), 6.75 (s, 1H), 4.31 (t, 2H), 3.83 (s, 3H), 3.69 (m, 1H), 3.38 (m, 4H), 3.32-3.20 (m, 6H), 2.61 (s, 6H), 2.35-2.25 (m, 2H), 1.88-1.80 (m, 2H). MS: m/z (MH) = 548.

**Example 9**

**(S)-(-)-1-[5-(6-Methylpyridin-2-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (E9)**

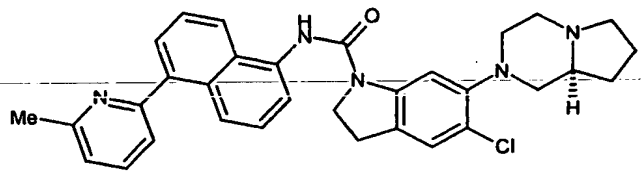



The title compound was prepared from 5-(6-methylpyridin-2-yl)-1-naphthoic acid (D9, 290 mg, 1.1mmole) and (S)-(-)-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D31, 180 mg, 0.74mmole) according to the procedure in Example 2 (200 mg, 54%).

$^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.97 (dd, 1H), 7.87 (d, 1H), 7.80-7.77 (m, 2H), 7.71 (dd, 1H), 7.60-7.58 (m, 2H), 7.46 (dd, 1H), 7.34 (d, 1H), 7.21 (dd, 1H), 7.07 (d, 1H), 6.80 (s, 1H), 6.56 (dd, 1H), 4.25 (t, 2H), 3.77 (d 1H), 3.62 (d, 1H), 3.23 (t, 2H), 3.11-3.08 (m, 2H), 2.89 (dt, 1H), 2.67 (s, 3H), 2.52 (t, 1H), 2.34 (dt, 1H), 2.16-2.11 (m, 2H), 1.90-1.72 (m, 3H), 1.49-1.41 (m, 1H). MS: m/z (MH) = 504.

**Example 10**

**(S)-(-)-5-Chloro-1-[5-(6-methylpyridin-2-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (E10)**

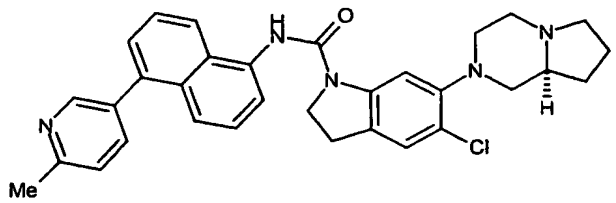


A suspension of 5-(6-methylpyridin-2-yl)-1-naphthoic acid (D9, 178 mg, 0.68 mmole) in dry toluene (30 ml) was treated with triethylamine (0.11 ml, 0.81 mmole) and stirred at room temperature, under argon, until all material was in solution (~ 5 minutes). Diphenylphosphoryl azide (0.16 ml, 0.74 mmole) was then added and the mixture heated under reflux, under argon, for 30 minutes, then cooled to ambient temperature and treated with a solution of (S)-(-)-5-chloro-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D34, 150 mg, 0.54 mmole) in DCM (10 ml). After 18 hours, the solvents were removed *in vacuo* and the residue purified by column chromatography on basic alumina, eluting with $Et_2O$-EtOAc gradient, to afford the title compound as a beige solid (260 mg, 89%). This was converted to its hydrochloride salt as a pale yellow solid from acetone.

$^1H$ NMR (free base) (250 MHz, $CDCl_3$) δ (ppm): 7.98 (dd, 1H), 7.91-7.87 (m, 2H), 7.77-7.69 (m, 2H), 7.62-7.55 (m, 2H), 7.46 (dd, 1H), 7.34 (d, 1H), 7.22 (d, 1H), 7.17 (s, 1H), 6.74 (s, 1H), 4.26 (t, 2H), 3.40 (br d, 2H), 3.26 (t, 2H), 3.12-3.03 (m, 2H), 2.82 (dt, 1H), 2.68 (s, 3H), 2.60 (t, 1H), 2.47 (dt, 1H), 2.25-2.18 (m, 2H), 1.88-1.61 (m, 3H), 1.42-1.32 (m, 1H). MS: m/z (MH) = 538, 540.

**Example 11**

**(S)-(-)-5-Chloro-1-[5-(6-methylpyridin-3-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (E11)**

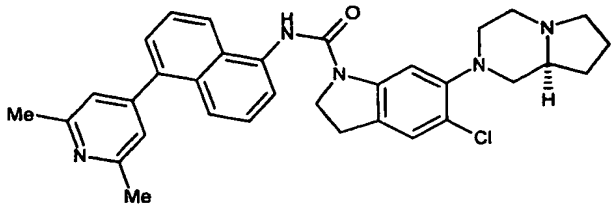


The title compound was prepared from 5-(6-methylpyridin-3-yl)-1-naphthoic acid (D35, 178 mg, 0.68 mmole) and (S)-(-)-5-chloro-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-

yl)indoline (D34, 150 mg, 0.54 mmole) according to the procedure in Example 10 (172 mg, 59%). This was converted to its hydrochloride salt as a beige solid from acetone.
$^1$H NMR (free base) (250 MHz, $CDCl_3$) δ (ppm): 8.62 (d, 1H), 7.99 (d, 1H), 7.86 (s, 1H), 7.77-7.68 (m, 3H), 7.60 (dd, 1H), 7.50-7.42 (m, 2H), 7.30 (d, 1H), 7.19 (s, 1H), 6.71 (s, 1H), 4.29 (t, 2H), 3.41 (br d, 2H), 3.28 (t, 2H), 3.12-3.02 (m, 2H), 2.82 (dt, 1H), 2.68 (s, 3H), 2.63-2.54 (m, 1H), 2.46 (dt, 1H), 2.30-2.15 (m, 2H), 1.87-1.66 (m, 3H), 1.50-1.47 (m, 1H). MS: m/z (MH) = 538, 540.

**Example 12**

**(S)-(-)-5-Chloro-1-[5-(2,6-dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (E12)**




The title compound was prepared from 5-(2,6-dimethylpyridin-4-yl)-1-naphthoic acid (D12, 178 mg, 0.64 mmole) and (S)-(-)-5-chloro-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline (D34, 150 mg, 0.54 mmole) according to the procedure in Example 10 (222 mg, 74%). This was converted to its hydrochloride salt as a pale yellow solid from acetone.
$^1$H NMR (free base) (250 MHz, $CDCl_3$) δ (ppm): 7.99 (d, 1H), 7.86 (s, 1H), 7.78-7.70 (m, 2H), 7.58 (dd, 1H), 7.49 (d, 1H), 7.41 (d, 1H), 7.19 (s, 1H), 7.08 (s, 2H), 6.70 (s, 1H), 4.29 (t, 2H), 3.40 (br d, 2H), 3.28 (t, 2H), 3.12-3.00 (m, 2H), 2.81 (dt, 1H), 2.62 (s, 6H), 2.65-2.54 (m, 1H), 2.45 (dt, 1H), 2.31-2.17 (m, 2H), 1.86-1.66 (m, 3H), 1.47-1.37 (m, 1H). MS: m/z (MH) = 552, 554.

**Pharmacological Data**

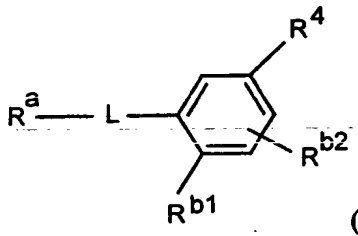
The affinities of the compounds of this invention were determined by methods described above.

5-$HT_{1A}$, 5-$HT_{1B}$ and 5-$HT_{1D}$ Receptor Binding

All examples had pKi values > 7.4 at 5-$HT_{1A}$, 5-$HT_{1B}$ and 5-$HT_{1D}$ receptors.

## CLAIMS

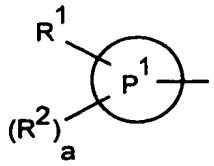
1. A compound of formula (I) or a salt thereof:



(I)

in which $R^a$ is selected from a group of formula (i), (ii) or (iii):

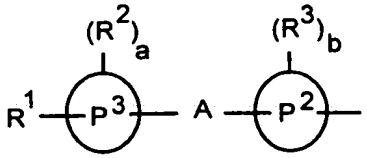
Group of formula (i)



(i)

in which $P^1$ is phenyl, bicyclic aryl, a 5- to 7- membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur or a bicyclic heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur;
$R^1$ is hydrogen, halogen, $C_{1-6}$alkyl, $C_{3-6}$cycloalkyl, $C_{1-6}$alkanoyl, $C_{1-6}$alkoxy, hydroxy, hydroxy$C_{1-6}$alkyl, hydroxy$C_{1-6}$alkoxy, $C_{1-6}$alkoxy$C_{1-6}$alkoxy, nitro, trifluoromethyl, cyano, $SR^9$, $SOR^9$, $SO_2R^9$, $SO_2NR^{10}R^{11}$, $CO_2R^{10}$, $CONR^{10}R^{11}$, $CONR^{10}(CH_2)_cCO_2R^{11}$, $(CH_2)_cNR^{10}R^{11}$, $(CH_2)_cCONR^{10}R^{11}$, $(CH_2)_cNR^{10}COR^{11}$, $(CH_2)_cCO_2C_{1-6}$alkyl, $CO_2(CH_2)_cOR^{10}$, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CONR^{10}R^{11}$, $CR^{10}{=}NOR^{11}$ where $R^9$, $R^{10}$ and $R^{11}$ are independently hydrogen or $C_{1-6}$alkyl and c is 1 to 4;
$R^2$ is halogen, $C_{1-6}$alkyl, $C_{3-6}$cycloalkyl, $C_{3-6}$cycloalkenyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, aryl, -OC(O)$C_{1-6}$alkyl, hydroxy, nitro, trifluoromethyl, cyano, $CO_2R^{10}$, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ where $R^{10}$ and $R^{11}$ are as defined for $R^1$;
a is 0, 1 or 2;

Group of formula (ii)



(ii)

wherein $P^2$ and $P^3$ are independently phenyl, bicyclic aryl, a 5- to 7- membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a bicyclic heterocyclic group containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur;

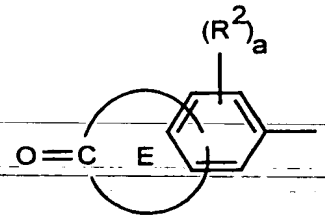
A is a bond or oxygen, $S(O)_n$ where n is 0 to 2, carbonyl, $CH_2$ or $NR^4$ where $R^4$ is hydrogen or $C_{1-6}$alkyl;

$R^1$ is as defined above for formula (i) or is a 5 to 7-membered heterocyclic ring, containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur, optionally substituted by $C_{1-6}$alkyl, halogen or $C_{1-6}$alkanoyl;

$R^2$ and $R^3$ are as defined above for $R^2$ in formula (i);

and a and b are independently 0, 1 or 2;

Group of formula (iii)



(iii)

in which the ring E is a 5, 6 or 7 -membered carbocyclic ring optionally substituted by one or more $C_{1-6}$alkyl groups, fused at the 2,3- or 3,4-positions of the adjacent phenyl ring, the ring E being optionally fused to a further phenyl ring optionally substituted by one or more substituents independently selected from $C_{1-6}$alkyl and halo;

a is 0, 1 or 2; and

$R^2$ is as defined above for formula (i);

L is a group of formula

- C (=V) - DG - or - DG - C(=V) - or -Y-C(=V)-DG-

V is oxygen or sulphur;

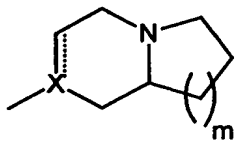
Y is -NH- or $-NR^5-$ where $R^5$ is $C_{1-6}$alkyl, or Y is $-CH_2-$ or -O-;

D is nitrogen, carbon or a CH group, G is hydrogen or $C_{1-6}$alkyl, providing that D is nitrogen or a CH group, or G together with $R^{b1}$ forms a group W where W is $(CR^{16}R^{17})_t$ where t is 2, 3 or 4 and $R^{16}$ and $R^{17}$ are independently hydrogen or $C_{1-6}$alkyl or W is $(CR^{16}R^{17})_u$-J where u is 0, 1, 2 or 3 and J is oxygen, sulphur,

$CR^{16}=CR^{17}$, $CR^{16}=N$, $=CR^{16}O$, $=CR^{16}S$ or $=CR^{16}-NR^{17}$ provided that u is not 0 when J is oxygen or sulphur;

$R^{b1}$ and $R^{b2}$ are independently hydrogen, halogen, hydroxy, $C_{1-6}$alkyl, trifluoromethyl, $C_{1-6}$alkoxy or aryl, or $R^{b1}$ together with G forms a group W as defined above;

$R^4$ is a group of formula (a) optionally substituted by $C_{1-6}$alkyl;



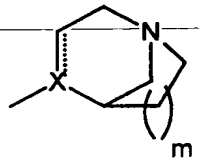
(a)

in which X is nitrogen, carbon or a CH,

..... is a single bond when X is nitrogen or CH and is a double bond when X is carbon,

m is 1, 2 or 3 ;

or $R^4$ is a group of formula (b) optionally substituted by $C_{1-6}$alkyl;



(b)

in which ....., X and m are as defined in formula (a);

2. A compound according to claim 1 in which one of $P^1$, $P^2$ and/or $P^3$ is a naphthyl group.

3. A compound according to claim 1 or 2 in which $R^a$ is a group of formula (ii) wherein $P^2$ is naphthyl and $P^3$ is pyridyl.

4. A compound according to any the preceding claims in which V is oxygen, D is nitrogen and G is hydrogen or together with $R^{b1}$ forms a $-(CH_2)_2-$ group.

5. A compound according to any the preceding claims in which $R^{b2}$ is hydrogen, halogen or $C_{1-6}$alkoxy with a para relationship with respect to the group $R^a$-L.

6. A compound according to any the preceding claims in which X is nitrogen.

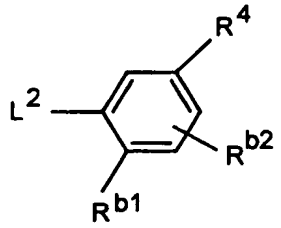
7. A compound according to claim 1 which is:
N-[(S)-4-Methoxy-3-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)phenyl]-N'-[4-(pyridin-4-yl)naphth-1-yl]-urea,
(S)-(-)-5-Methoxy-1-[5-(6-methylpyridin-2-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline,
(S)-(-)-5-Methoxy-1-[5-(2-methylpyridin-3-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline,
(S)-(-)-1-[5-(2,6-Dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-5-methoxy-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline,
(S)-(-)-1-[5-(2,6-Dimethylpyridin-3-yl)naphth-1-ylaminocarbonyl]-5-methoxy-6-(octahydropyrrolo[1,2-a]pyrazin-2-yl)indoline,
(R)-(+)-1-[5-(2,6-Dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-5-methoxy-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline
(R/S)-(+/-)-1-[5-(2,6-Dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-5-methoxy-6-(octahydropyrido[1,2-*a*]pyrazin-2-yl)indoline,
6-(1,4-Diazabicyclo[3.2.2]non-4-yl)-1-[5-(2,6-dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-5-methoxyindoline,
(S)-(-)-1-[5-(6-Methylpyridin-2-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline,
(S)-(-)-5-Chloro-1-[5-(6-methylpyridin-2-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline,
(S)-(-)-5-Chloro-1-[5-(6-methylpyridin-3-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline,
(S)-(-)-5-Chloro-1-[5-(2,6-dimethylpyridin-4-yl)naphth-1-ylaminocarbonyl]-6-(octahydropyrrolo[1,2-*a*]pyrazin-2-yl)indoline
and pharmaceutically acceptable salt thereof.

8. A process for the preparation of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof which comprises:
(a) where L is - C (=V) - DG - or - DG - C(=V) -, coupling a compound of formula (II):

$$R^a\text{-}L^1$$

(II)

with a compound of formula (III).



(III)

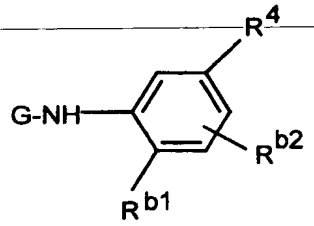
in which $R^a$, $R^{b1}$, $R^{b2}$, $R^4$ are as defined in formula (I) and $L^1$ and $L^2$ contain the appropriate functional groups which are capable of reacting together to form the L moiety; or

(b) where L is - Y -C(=V)-DG in which D is nitrogen and Y is NH, coupling a compound of formula (IV):

$$R^a\text{-}NC(=V)$$

(IV)

in which $R^a$ and V are as defined in formula (I) or a protected derivative thereof with a compound of formula (V):



(V)

in which $R^{b1}$ , $R^{b2}$, $R^4$, G are as defined in formula (I), or a protected derivative thereof; or

(c) where L is - Y -C(=V)-$DG^1$ - in which D is nitrogen and Y is NH or $NR^5$, reacting a compound of formula (VI)

$$R^a\text{-}NH_2 \text{ or } R^a\text{-}NR^5H$$

(VI)

in which $R^a$ and $R^5$ are as defined in formula (I) with a compound of formula (V) together with an appropriate urea forming agent; or

(d) where L is - Y -C(=V)-DG - in which D is nitrogen and Y is $CH_2$ or O, reacting a compound of formula (VII)

$$R^a\text{-}Y\text{-}(C{=}O)\text{-}L^3$$

(VII)

in which $R^a$ is as defined in formula (I),

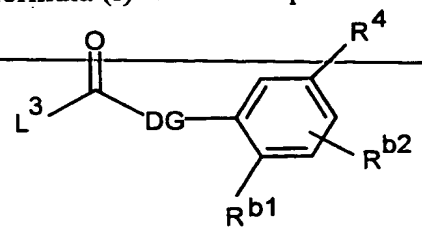
and $L^3$ is an appropriate leaving group, with a compound of formula (V); or

(e) where L is - Y -C(=V)-DG – in which D is CH, reacting a compound of formula (VI)

$$R^a\text{-}NH_2$$

(VI)

in which $R^a$ is as defined in formula (I) with a compound of formula (VIII)




(VIII)

in which D is CH, and G, $R^4$, $R^{b1}$ and $R^{b2}$ are as defined in formula (I) and $L^3$ is an appropriate leaving atom and optionally thereafter:

- removing any protecting groups,
- converting a compound of formula (I) into another compound of formula (I),
- forming a pharmaceutically acceptable salt.

9. A compound according to any of claims 1 to 7 for use in therapy.

10. A compound according to any of claims 1 to 7 for use in treatment of depression.

11. A pharmaceutical composition which comprises a compound according to any of claims 1 to 7 and a pharmaceutically acceptable carrier.

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classificati n [7]:
**C07D 487/04**
*(Continued on the following page)*

**A3**

(11) International Publicati n Number: **WO 00/06575**

(43) Internati nal Publicati n Date: 10 February 2000 (10.02.00)

(21) International Application Number: PCT/EP99/05350

(22) International Filing Date: 23 July 1999 (23.07.99)

(30) Priority Data:

| | | |
|---|---|---|
| 9816288.6 | 28 July 1998 (28.07.98) | GB |
| 9827881.5 | 17 December 1998 (17.12.98) | GB |

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

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(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

**Published**
*With international search report.*
*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(88) Date of publication of the international search report:
18 May 2000 (18.05.00)

(54) Title: AZABICYCLIC COMPOUNDS

(57) Abstract

The invention relates to novel azabicyclic compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS disorders.

**(51) International Patent Classification [7]:**

**A61K 31/4985, 31/551, C07D 471/04, 471/08, A61P 25/00, C07D 487/08, 455/02 // (C07D 487/04, 241:00 209:00), (C07D 471/04, 241:00, 221:00), (C07D 471/08, 243:00, 221:00)**

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# INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 99/05350

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/4985 A61K31/551 C07D471/04 C07D471/08 A61P25/00 C07D487/08 C07D455/02 //(C07D487/04,241:00, 209:00),(C07D471/04,241:00,221:00),(C07D471/08,243:00,221:00)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 95 06044 A (SMITHKLINE BEECHAM PLC ) 2 March 1995 (1995-03-02) cited in the application page 7, line 36 -page 8, line 12; claim 1 --- | 1,11 |
| A | WO 95 06637 A (SMITHKLINE BEECHAM PLC) 9 March 1995 (1995-03-09) cited in the application page 7, line 21 - line 34; claim 1 --- | 1,11 |
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 15 March 2000 | 29/03/2000 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Alfaro Faus, I |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/05350

## B x I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: none
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: none

Present claims 1 to 11 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula I, where L is urea group '-HNC(O)N=! , as described in examples 1 to 12.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int .tional Application No
PCT/EP 99/05350

| Patent document cited in s arch report | Publication date | Patent family member(s) | Publication date |
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